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FILING DATE: February 11, 2004

RELATED PCT APPLICATION NUMBER: PCT/US05/04655



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PTO/SB/15 (10-01)

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PROVISIONAL APPLICATION FOR PATENT COVER SHEETThis is a request for filing a **PROVISIONAL APPLICATION FOR PATENT** under 37 CFR 1.53 (c).

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60/543848

021104

INVENTOR(S)				
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<input checked="" type="checkbox"/> Additional inventors are being named on the 1 separately numbered sheets attached hereto				
TITLE OF THE INVENTION (500 characters max)				
COMPOUNDS AND COMPOSITIONS AS LXR MODULATORS				
CORRESPONDENCE ADDRESS				
Direct all correspondence to:		Place Customer Number Bar Code Label here		
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ENCLOSED APPLICATION PARTS (check all that apply)				
<input checked="" type="checkbox"/> Specification Number of Pages	32	<input type="checkbox"/> CD(s), Number		
<input type="checkbox"/> Drawing(s) Number of Sheets		<input checked="" type="checkbox"/> Other (specify)	RETURN POSTCARD AND FEE TRANSMITTAL	
<input type="checkbox"/> Application Data Sheet. See 37 CFR 1.76				
METHOD OF PAYMENT OF FILING FEES FOR THIS PROVISIONAL APPLICATION FOR PATENT				
<input type="checkbox"/> Applicant claims small entity status. See 37 CFR 1.27.		FILING FEE AMOUNT (\$)		
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Respectfully submitted,

SIGNATURE

Date

2/11/04

TYPED or PRINTED NAME

Scott W. Reid

REGISTRATION NO.

48,097

(if appropriate)

Docket Number:

P1132US10

TELEPHONE

858-812-1796

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Docket Number		P1132US10
INVENTOR(S)/APPLICANT(S)		
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Number 1 of 1

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FEE TRANSMITTAL for FY 2003

Effective 01/01/2003. Patent fees are subject to annual revision.

☐ Applicant claims small entity status. See 37 CFR 1.27

TOTAL AMOUNT OF PAYMENT (\$) 160

Complete If Known

Application Number

Filing Date

11 February 2004

First Named Inventor

Valentina MOLTEINI

Examiner Name

Art Unit

Attorney Docket No. P1132US10

METHOD OF PAYMENT (check all that apply)

☐ Check ☐ Credit card ☐ Money ☐ Other ☐ None

☒ Deposit Account.

Deposit
Account
Number

50-1885

Deposit
Account
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The Genomics Institute of the Novartis Research
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The Director is authorized to: (check all that apply)

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FEE CALCULATION

1. BASIC FILING FEE

Large Entity Fee Code	Fee (\$)	Small Entity Fee Code	Fee (\$)	Fee Description	Fee Paid
1001	750	2001	375	Utility filing fee	160
1002	330	2002	165	Design filing fee	
1003	520	2003	260	Plant filing fee	
1004	750	2004	375	Reissue filing fee	
1005	180	2005	80	Provisional filing fee	

SUBTOTAL (1)

(\$ 160)

2. EXTRA CLAIM FEES

Large Entity Fee Code	Fee (\$)	Small Entity Fee Code	Fee (\$)	Fee Description	Fee Paid
1202	18	2202	9	Claims in excess of 20	
1201	84	2201	42	Independent claims in excess of 3	
1203	280	2203	140	Multiple dependent claim, if not paid	
1204	84	2204	42	** Reissue independent claims over original patent	
1205	18	2205	9	** Reissue claims in excess of 20 and over original patent	

SUBTOTAL (2) (\$ 0)

**or number previously paid, if greater; For Reissues, see above

FEE CALCULATION (continued)

3. ADDITIONAL FEES

Large Entity Fee Code	Fee (\$)	Small Entity Fee Code	Fee (\$)	Fee Description	Fee Paid
1051	130	2051	65	Surcharge - late filing fee or oath	
1052	50	2052	25	Surcharge - late provisional filing fee or cover sheet	
1053	130	2053	65	Non-English specification	
1812	2,520	1812	2,520	For filing a request for reexamination	
1804	920*	1804	920*	Requesting publication of SIR prior to Examiner action	
1805	1,840*	1805	1,840*	Requesting publication of SIR after Examiner action	
1251	110	2251	55	Extension for reply within first month	
1252	410	2252	205	Extension for reply within second month	
1253	930	2253	465	Extension for reply within third month	
1254	1,450	2254	725	Extension for reply within fourth month	
1255	1,970	2255	985	Extension for reply within fifth month	
1401	320	2401	160	Notice of Appeal	
1402	320	2402	160	Filing a brief in support of an appeal	
1403	280	2403	140	Request for oral hearing	
1451	1,510	1451	1,510	Petition to institute a public use proceeding	
1452	110	2452	55	Petition to revive - unavoidable	
1453	1,300	2453	650	Petition to revive - unintentional	
1501	1,300	2501	650	Utility issue fee (or reissue)	
1502	470	2502	235	Design issue fee	
1503	630	2503	315	Plant issue fee	
1460	130	1460	130	Petitions to the Commissioner	
1807	50	1807	50	Processing fee under 37 CFR 1.17 (q)	
1806	180	1806	180	Submission of Information Disclosure Stmt	
8021	40	8021	40	Recording each patent assignment per property (times number of properties)	
1809	750	2809	375	Filing a submission after final rejection (37 CFR § 1.129(a))	
1810	750	2810	375	For each additional invention to be examined (37 CFR § 1.129(b))	
1801	750	2801	375	Request for Continued Examination (RCE)	
1802	900	1802	900	Request for expedited examination of a design application	

Other fee (specify) _____

*Reduced by Basic Filing Fee Paid

SUBTOTAL (3)

(\$ 0)

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Date

11 February 2004

Complete (if applicable)

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I hereby certify that this is being deposited with the United States Postal Service "Express Mail Post Office to Addressee" service under 37 CFR 1.10 on the date indicated above, addressed to: Mail Stop Provisional Patent Application, Commissioner for Patents PO Box 1450, Alexandria, VA 22313-1450

By: Scott W. Reid

Scott W. Reid

Docket No: P1132US10

United States Provisional Patent Application

**COMPOUNDS AND COMPOSITIONS AS
LXR MODULATORS**

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COMPOUNDS AND COMPOSITIONS AS LXR MODULATORS

BACKGROUND OF THE INVENTION

Field of the Invention

The invention provides compounds, pharmaceutical compositions comprising such compounds and methods of using such compounds to treat or prevent diseases or disorders associated with the activity of liver X receptors (LXRs).

Background

Liver X receptors (LXRs), LXR α and LXR β , are nuclear receptors that regulate the metabolism of several important lipids, including cholesterol and bile acids. While LXR β is expressed ubiquitously in the body, LXR α is expressed in the liver and to a smaller degree in the kidneys, small intestine, adipose tissue, spleen and adrenal glands.

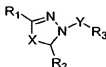
LXRs bind to the ATP binding cassette transporter-1 (ABCA1) promoter and increase expression of the gene to produce ABCA1 protein. ABCA1 is a membrane bound transport protein that is involved in the regulation of cholesterol efflux from extra-hepatic cells onto nascent high-density lipoprotein (HDL) particles. Mutations in the ABCA1 gene result in low levels of HDL and an accompanying increased risk of cardiovascular diseases such as atherosclerosis, myocardial infarction and ischemic stroke. LXR α and β agonists have been shown to increase ABCA1 gene expression thereby increasing HDL cholesterol and, as a consequence, decreasing both the absorption of cholesterol and the risk of cardiovascular disease. LXR agonists also upregulate macrophage expression of apolipoprotein E (apoE) and ABCG1, both of which contribute to the efflux of cellular cholesterol. By stimulating macrophage cholesterol efflux through upregulation of ABCA1, ABCG1 and/or apoE expression, as well as increasing the expression of other target genes including cholesterol ester transfer protein and lipoprotein lipase, LXR agonists influence plasma lipoproteins.

The novel compounds of this invention modulate the activity of LXRs and are, therefore, expected to be useful in the treatment of LXR-associated diseases such as cardiovascular diseases, inflammation and disorders of glucose metabolism such as insulin resistance and obesity.

5

SUMMARY OF THE INVENTION

In one aspect, the present invention provides compounds of Formula I:



10

in which:

X is selected from the group consisting of S, O and CR₄R₅; wherein R₄ is selected from the group consisting of hydrogen and C₁₋₆alkyl; R₅ is selected from the group consisting of hydrogen, C₁₋₆alkyl, C₆₋₁₀aryl, C₅₋₁₀heteroaryl, C₃₋₁₂cycloalkyl and C₃₋₈heterocycloalkyl; or R₄ and R₅ together with the carbon atom to which R₄ and R₅ are attached. form C₃₋₁₂cycloalkyl or C₃₋₈heterocycloalkyl; wherein any aryl, heteroaryl, cycloalkyl or heterocycloalkyl of R₅ or the combination of R₄ and R₅ is optionally substituted with 1 to 4 radicals independently selected from the group consisting of halo, hydroxy, cyano, nitro, C₁₋₆alkyl, C₁₋₆alkoxy, halo-substituted-C₁₋₆alkyl and halo-substituted-C₁₋₆alkoxy;

15

Y is selected from the group consisting of C(O), S(O), S(O)₂, C(O)N(R₆) and C(O)OR₆; wherein R₆ is selected from the group consisting of hydrogen, C₁₋₆alkyl, C₆₋₁₀aryl, C₅₋₁₀heteroaryl, C₃₋₁₂cycloalkyl and C₃₋₈heterocycloalkyl; wherein any aryl, heteroaryl, cycloalkyl or heterocycloalkyl of R₆ is optionally substituted with 1 to 4 radicals independently selected from the group consisting of halo, hydroxy, cyano, nitro, C₁₋₆alkyl, C₁₋₆alkoxy, halo-substituted-C₁₋₆alkyl and halo-substituted-C₁₋₆alkoxy;

20

R₁ is selected from the group consisting of C₆₋₁₀aryl, C₅₋₁₀heteroaryl, C₃₋₁₂cycloalkyl and C₃₋₈heterocycloalkyl; wherein any aryl, heteroaryl, cycloalkyl or heterocycloalkyl of R₁ is optionally substituted with 1 to 4 radicals independently selected from the group consisting of halo, hydroxy, cyano, nitro, C₁₋₆alkyl, C₁₋₆alkoxy, halo-substituted-C₁₋₆alkyl, halo-substituted-C₁₋₆alkoxy -C(O)NR₇R₇, -OC(O)R₇, -NR₇R₈, -C(O)R₇ and -NR₇C(O)R₇; wherein R₇ and R₈ are

25

independently chosen from hydrogen, C₁₋₆alkyl, C₁₋₆alkoxy, halo-substituted-C₁₋₆alkyl and halo-substituted-C₁₋₆alkoxy, C₆₋₁₀aryl-C₀₋₄alkyl, C₃₋₈heteroaryl-C₀₋₄alkyl, C₃₋₁₂cycloalkyl-C₀₋₄alkyl and C₃₋₈heterocycloalkyl-C₀₋₄alkyl; or R₇ and R₈ together with the nitrogen atom to which R₇ and R₈ are attached form C₅₋₁₀heteroaryl or C₃₋₈heterocycloalkyl; wherein any aryl, heteroaryl,

5 cycloalkyl or heterocycloalkyl of R₇ or the combination of R₇ and R₈ is optionally substituted with 1 to 4 radicals independently selected from the group consisting of halo, hydroxy, cyano, nitro, C₁₋₆alkyl, C₁₋₆alkoxy, halo-substituted-C₁₋₆alkyl and halo-substituted-C₁₋₆alkoxy;

R₂ is selected from the group consisting of C₆₋₁₀aryl, C₅₋₁₀heteroaryl, C₃₋₁₂cycloalkyl and C₃₋₈heterocycloalkyl; wherein any aryl, heteroaryl, cycloalkyl or

10 heterocycloalkyl of R₂ is optionally substituted with 1 to 4 radicals independently selected from the group consisting of halo, hydroxy, cyano, nitro, C₁₋₆alkyl, C₁₋₆alkoxy, halo-substituted-C₁₋₆alkyl, halo-substituted-C₁₋₆alkoxy -C(O)NR₇R₈, -OR₇, -OC(O)R₇, -NR₇R₈, -C(O)R₇ and -NR₇C(O)R₇; wherein R₇ and R₈ are independently chosen from hydrogen, C₁₋₆alkyl, C₁₋₆alkoxy, halo-substituted-C₁₋₆alkyl and halo-substituted-C₁₋₆alkoxy, C₆₋₁₀aryl-C₀₋₄alkyl, C₃₋₈heteroaryl-C₀₋₄alkyl, C₃₋₁₂cycloalkyl-C₀₋₄alkyl and C₃₋₈heterocycloalkyl-C₀₋₄alkyl; or R₇ and R₈ together with the nitrogen atom to which R₇ and R₈ are attached form C₅₋₁₀heteroaryl or C₃₋₈heterocycloalkyl;

15 wherein any aryl, heteroaryl, cycloalkyl or heterocycloalkyl of R₇ or the combination of R₇ and R₈ is optionally substituted with 1 to 4 radicals independently selected from the group consisting of halo, hydroxy, cyano, nitro, C₁₋₆alkyl, C₁₋₆alkoxy, halo-substituted-C₁₋₆alkyl and halo-substituted-C₁₋₆alkoxy;

R₃ is selected from the group consisting of C₆₋₁₀aryl, C₅₋₁₀heteroaryl, C₃₋₁₂cycloalkyl and C₃₋₈heterocycloalkyl; wherein any aryl, heteroaryl, cycloalkyl or heterocycloalkyl of R₃ is optionally substituted with 1 to 4 radicals independently selected from the group consisting of halo, hydroxy, cyano, nitro, C₁₋₆alkyl, C₁₋₆alkoxy, halo-substituted-C₁₋₆alkyl, halo-substituted-C₁₋₆alkoxy -C(O)NR₇R₈, -OC(O)R₇, -NR₇R₈, -C(O)R₇ and -NR₇C(O)R₇; wherein R₇ and R₈ are independently chosen from hydrogen, C₁₋₆alkyl, C₁₋₆alkoxy, halo-substituted-C₁₋₆alkyl and halo-substituted-C₁₋₆alkoxy, C₆₋₁₀aryl-C₀₋₄alkyl, C₃₋₈heteroaryl-C₀₋₄alkyl, C₃₋₁₂cycloalkyl-C₀₋₄alkyl and C₃₋₈heterocycloalkyl-C₀₋₄alkyl; or R₇ and R₈ together with the nitrogen atom to which R₇ and R₈ are attached form C₅₋₁₀heteroaryl or C₃₋₈heterocycloalkyl;

25 wherein any aryl, heteroaryl, cycloalkyl or heterocycloalkyl of R₇ or the combination of R₇ and R₈ is optionally substituted with 1 to 4 radicals independently selected from the group consisting of halo, hydroxy, cyano, nitro, C₁₋₆alkyl, C₁₋₆alkoxy, halo-substituted-C₁₋₆alkyl and halo-substituted-C₁₋₆alkoxy, C₆₋₁₀aryl-C₀₋₄alkyl, C₃₋₈heteroaryl-C₀₋₄alkyl, C₃₋₁₂cycloalkyl-C₀₋₄alkyl and C₃₋₈heterocycloalkyl-C₀₋₄alkyl; or R₇ and R₈ together with the nitrogen atom to which R₇ and R₈ are attached form C₅₋₁₀heteroaryl or C₃₋₈heterocycloalkyl;

30 wherein any aryl, heteroaryl, cycloalkyl or heterocycloalkyl of R₇ or the combination of R₇ and R₈ is optionally substituted with 1 to 4 radicals independently selected from the group consisting

of halo, hydroxy, cyano, nitro, C₁₋₆alkyl, C₁₋₆alkoxy, halo-substituted-C₁₋₆alkyl and halo-substituted-C₁₋₆alkoxy; and the N-oxide derivatives, prodrug derivatives, protected derivatives, individual isomers and mixture of isomers thereof; and the pharmaceutically acceptable salts and solvates (e.g. hydrates) of such compounds.

5 In a second aspect, the present invention provides a pharmaceutical composition which contains a compound of Formula I or a N-oxide derivative, individual isomers and mixture of isomers thereof; or a pharmaceutically acceptable salt thereof, in admixture with one or more suitable excipients.

10 In a third aspect, the present invention provides a method of treating a disease in an animal in which modulation of LXR activity can prevent, inhibit or ameliorate the pathology and/or symptomology of the diseases, which method comprises administering to the animal a therapeutically effective amount of a compound of Formula I or a N-oxide derivative, individual isomers and mixture of isomers thereof, or a pharmaceutically acceptable salt thereof.

15 In a fourth aspect, the present invention provides the use of a compound of Formula I in the manufacture of a medicament for treating a disease in an animal in which LXR activity contributes to the pathology and/or symptomology of the disease.

20 In a fifth aspect, the present invention provides a process for preparing compounds of Formula I and the N-oxide derivatives, prodrug derivatives, protected derivatives, individual isomers and mixture of isomers thereof, and the pharmaceutically acceptable salts thereof.

DETAILED DESCRIPTION OF THE INVENTION

Definitions

25 "Alkyl" as a group and as a structural element of other groups, for example halo-substituted-alkyl and alkoxy, can be either straight-chained or branched. C₁₋₆alkoxy includes, methoxy, ethoxy, and the like. Halo-substituted alkyl includes trifluoromethyl, pentafluoroethyl, and the like.

"Aryl" means a monocyclic or fused bicyclic aromatic ring assembly containing six to ten ring carbon atoms. For example, aryl can be phenyl or naphthyl, preferably phenyl.

30 "Arylene" means a divalent radical derived from an aryl group. "Heteroaryl" is as defined for aryl where one or more of the ring members are a heteroatom. For example heteroaryl includes

pyridyl, indolyl, indazolyl, quinoxaliny, quinoliny, benzofuranyl, benzopyranyl, benzothiopyranyl, benzo[1,3]dioxole, imidazolyl, benzo-imidazolyl, pyrimidinyl, furanyl, oxazolyl, isoxazolyl, triazolyl, tetrazolyl, pyrazolyl, thienyl, etc.

“Cycloalkyl” means a saturated or partially unsaturated, monocyclic, fused bicyclic or bridged polycyclic ring assembly containing the number of ring atoms indicated. For example, C₃₋₁₀cycloalkyl includes cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, etc.

“Heterocycloalkyl” means cycloalkyl, as defined in this application, provided that one or more of the ring carbons indicated, are replaced by a moiety selected from -O-, -N=, -NR-, -C(O)-, -S-, -S(O)- or -S(O)₂-, wherein R is hydrogen, C₁₋₄alkyl or a nitrogen protecting group. For example, C₃₋₈heterocycloalkyl as used in this application to describe compounds of the invention includes morpholino, pyrrolidinyl, piperazinyl, piperidinyl, piperidinylone, 1,4-dioxo-8-aza-spiro[4.5]dec-8-yl, etc.

“Halogen” (or halo) preferably represents chloro or fluoro, but can also be bromo or iodo.

The term “modulate” with respect to an LXR receptor refers to activation of the LXR receptor and its biological activities associated with the LXR pathway (e.g., transcription regulation of a target gene). Modulation of LXR receptor can be up-regulation (i.e., agonizing, activation or stimulation) or down-regulation (i.e. antagonizing, inhibition or suppression). The mode of action of an LXR modulator can be direct, e.g., through binding to the LXR receptor as a ligand. The modulation can also be indirect, e.g., through binding to and/or modifying another molecule which otherwise binds to and activates the LXR receptor. Thus, modulation of LXR includes a change in the bioactivities of an LXR agonist ligand (i.e., its activity in binding to and/or activating an LXR receptor) or a change in the cellular level of the ligand.

“Treat”, “treating” and “treatment” refer to a method of alleviating or abating a disease and/or its attendant symptoms.

Description of the Preferred Embodiments

The present invention provides compounds, compositions and methods for the treatment of diseases in which modulation of LXR activity can prevent, inhibit or ameliorate the pathology and/or symptomology of the diseases, which method comprises administering to the animal a therapeutically effective amount of a compound of Formula I.

In one embodiment, with reference to compounds of Formula I, Y is selected from the group consisting of C(O) and S(O)₂ and R₁ is C₆₋₁₀aryl; wherein any aryl, heteroaryl, cycloalkyl or heterocycloalkyl of R₁ is optionally substituted with 1 to 4 radicals independently selected from the group consisting of halo, C₁₋₆alkyl, C₁₋₆alkoxy, halo-substituted-C₁₋₆alkyl and halo-substituted-C₁₋₆alkoxy.

In another embodiment, R₂ is selected from the group consisting of C₆₋₁₀aryl and C₃₋₁₀heteroaryl; wherein any aryl or heteroaryl of R₂ is optionally substituted with 1 to 3 radicals independently selected from the group consisting of halo, hydroxy, cyano, nitro, C₁₋₆alkyl, C₁₋₆alkoxy, halo-substituted-C₁₋₆alkyl and halo-substituted-C₁₋₆alkoxy.

In a further embodiment, R₃ is selected from the group consisting of C₆₋₁₀aryl and C₃₋₁₂cycloalkyl; wherein any aryl or cycloalkyl of R₃ is optionally substituted with 1 to 3 radicals independently selected from the group consisting of halo, -OC(O)R₇, C₁₋₆alkyl and C₁₋₆alkoxy; wherein R₇ is chosen from hydrogen, C₁₋₆alkyl, C₁₋₆alkoxy, halo-substituted-C₁₋₆alkyl and halo-substituted-C₁₋₆alkoxy, C₆₋₁₀aryl-C₀₋₄alkyl, C₃₋₈heteroaryl-C₀₋₄alkyl, C₃₋₁₂cycloalkyl-C₀₋₄alkyl and C₃₋₈heterocycloalkyl-C₀₋₄alkyl.

In another embodiment X is S.

In a further embodiment, R₁ is phenyl optionally substituted with 1 to 4 radicals independently selected from the group consisting of halo, C₁₋₆alkyl, C₁₋₆alkoxy, halo-substituted-C₁₋₆alkyl and halo-substituted-C₁₋₆alkoxy.

In another embodiment, R₂ is selected from the group consisting of phenyl and pyridinyl; wherein any aryl or heteroaryl of R₂ is optionally substituted with 1 to 3 radicals independently selected from the group consisting of halo, C₁₋₆alkyl, C₁₋₆alkoxy, halo-substituted-C₁₋₆alkyl and halo-substituted-C₁₋₆alkoxy.

In another embodiment, R₃ is selected from the group consisting of phenyl and cyclohexyl; wherein any aryl or cycloalkyl of R₃ is optionally substituted with 1 to 3 radicals independently selected from the group consisting of halo, -OC(O)CH₃, methyl, ethyl, propyl, isopropyl, butyl, tert-butyl and OCH₃.

Preferred compounds of Formula I are detailed in the Examples and Table I, *infra*.

Pharmacology and Utility

Compounds of the invention modulate the activity of LXRs and, as such, are useful for treating diseases or disorders in which LXRs contribute to the pathology and/or symptomology of the disease. This invention further provides compounds of this invention for use in the preparation of medicaments for the treatment of diseases or disorders in which LXRs contribute to the pathology and/or symptomology of the disease. LXR mediated diseases or conditions include inflammation, cardiovascular disease including atherosclerosis, arteriosclerosis, hypercholesteremia, hyperlipidemia and disorders of glucose homeostasis, including insulin resistance, type II diabetes, and obesity.

Lipoprotein metabolism is a dynamic process comprised of the production of triglyceride and cholesterol rich particles from the liver as very low-density lipoprotein (VLDL), modification of these lipoprotein particles within the plasma (VLDL to intermediate density (IDL) to low-density lipoprotein (LDL)) and clearance of the particles from the plasma, again by the liver. This process provides the transport of triglycerides and free cholesterol to cells of the body. Reverse cholesterol transport is the proposed mechanism by which excess cholesterol is returned to the liver from extra-hepatic tissue.

The process is carried out by high-density lipoprotein (HDL) cholesterol. The combination of lipoprotein production (VLDL, HDL) from the liver, modification of particles (all) within the plasma and subsequent clearance back to the liver, accounts for the steady state cholesterol concentration in plasma. Compounds of this invention increase reverse cholesterol transport by increasing cholesterol efflux from the arteries. This invention includes the use of compounds of this invention for the preparation of a medicament for increasing reverse cholesterol transport. Additionally, this invention provides compounds for inhibiting cholesterol absorption and the use of compounds of this invention for the preparation of a medicament for inhibiting cholesterol absorption.

The compounds of this invention can also be useful for the prevention or treatment of inflammation and neurodegenerative diseases or neurological disorders. Accordingly, this invention also provides a method for preventing or treating inflammation and a method for preventing or treating neurodegenerative diseases or neurological disorders, particularly neurodegenerative diseases or disorders characterized by neuron degeneration, neuron injury or impaired plasticity or inflammation in the CNS. Particular diseases or conditions that are

characterized by neuron degeneration and inflammation, and thus benefiting from the growth and/or repair of neurons include stroke, Alzheimer's disease, fronto-temporal dementias (taupathies), peripheral neuropathy, Parkinson's disease, dementia with Lewy bodies, Huntington's disease, amyotrophic lateral sclerosis and multiple sclerosis. Diseases or conditions that are characterized by neuron degeneration and/or impaired plasticity include psychiatric disorders such as schizophrenia and depression. Particular diseases or conditions that are characterized by neuronal injury include those conditions associated with brain and/or spinal cord injury, including trauma. In addition, the compounds of this invention can be used to treat or prevent various diseases with an inflammatory component, such as rheumatoid arthritis, osteoarthritis, psoriasis, asthma, etc.

LXR agonists improve glucose tolerance and enhance glut4 expression (U.S. Provisional Patent Application 60/436,112, filed 12/23/2002). There is a coordinated regulation of genes involved in glucose metabolism in liver and adipose tissue. In the liver, LXR agonists inhibit expression of several genes that are important for hepatic gluconeogenesis, e.g., PGC-1, phosphoenolpyruvate carboxykinase (PEPCK), and glucose-6-phosphatase expression. Inhibition of these gluconeogenic genes is accompanied by an induction in expression of glucokinase, which promotes hepatic glucose utilization. It was also found that glut4 mRNA levels were upregulated by LXR agonists in adipose tissue, and that glucose uptake in 3T3-L1 adipocytes was enhanced in vitro.

In accordance with these discoveries, the present invention provides methods for enhancing glut4 expression in cells in a subject by administering a compound of the invention to the subject. The present invention also provides methods for treating diabetes mellitus and related disorders, such as obesity or hyperglycemia, by administering to a subject an effective amount of a compound of the invention to ameliorate the symptoms of the disease. For example, type II diabetes is amenable to treatment with methods of the present invention. By enhancing sensitivity to insulin and glucose uptake by cells, administration with a compound of the invention can also treat other diseases characterized by insulin dysfunction (e.g., resistance, inactivity or deficiency) and/or insufficient glucose transport into cells.

Compounds of the present invention also regulate expression levels of a number of genes that play important roles in liver gluconeogenesis. Accordingly, the present invention

further provides methods for reducing gluconeogenesis in a subject by modulating expression of such genes (e.g., PGC-1 and PEPCK).

In accordance with the foregoing, the present invention further provides a method for preventing or treating any of the diseases or disorders described above in a subject in need of such treatment, which method comprises administering to said subject a therapeutically effective amount (See, "Administration and Pharmaceutical Compositions", *infra*) of a compound of Formula I or a pharmaceutically acceptable salt thereof. For any of the above uses, the required dosage will vary depending on the mode of administration, the particular condition to be treated and the effect desired.

Administration and Pharmaceutical Compositions

In general, compounds of the invention will be administered in therapeutically effective amounts via any of the usual and acceptable modes known in the art, either singly or in combination with one or more therapeutic agents. A therapeutically effective amount can vary widely depending on the severity of the disease, the age and relative health of the subject, the potency of the compound used and other factors. In general, satisfactory results are indicated to be obtained systemically at daily dosages of from about 0.03 to 2.5mg/kg per body weight. An indicated daily dosage in the larger mammal, e.g. humans, is in the range from about 0.5mg to about 100mg, conveniently administered, e.g. in divided doses up to four times a day or in retard form. Suitable unit dosage forms for oral administration comprise from ca. 1 to 50mg active ingredient.

Compounds of the invention can be administered as pharmaceutical compositions by any conventional route, in particular enterally, e.g., orally, e.g., in the form of tablets or capsules, or parenterally, e.g., in the form of injectable solutions or suspensions, topically, e.g., in the form of lotions, gels, ointments or creams, or in a nasal or suppository form. Pharmaceutical compositions comprising a compound of the present invention in free form or in a pharmaceutically acceptable salt form in association with at least one pharmaceutically acceptable carrier or diluent can be manufactured in a conventional manner by mixing, granulating or coating methods. For example, oral compositions can be tablets or gelatin capsules comprising the active ingredient together with a) diluents, e.g., lactose, dextrose, sucrose, mannitol, sorbitol, cellulose and/or glycine; b) lubricants, e.g., silica, talcum, stearic

acid, its magnesium or calcium salt and/or polyethyleneglycol; for tablets also c) binders, e.g., magnesium aluminum silicate, starch paste, gelatin, tragacanth, methylcellulose, sodium carboxymethylcellulose and or polyvinylpyrrolidone; if desired d) disintegrants, e.g., starches, agar, alginic acid or its sodium salt, or effervescent mixtures; and/or e) absorbents, colorants, flavors and sweeteners. Injectable compositions can be aqueous isotonic solutions or suspensions, and suppositories can be prepared from fatty emulsions or suspensions. The compositions can be sterilized and/or contain adjuvants, such as preserving, stabilizing, wetting or emulsifying agents, solution promoters, salts for regulating the osmotic pressure and/or buffers. In addition, they can also contain other therapeutically valuable substances. Suitable formulations for transdermal applications include an effective amount of a compound of the present invention with a carrier. A carrier can include absorbable pharmacologically acceptable solvents to assist passage through the skin of the host. For example, transdermal devices are in the form of a bandage comprising a backing member, a reservoir containing the compound optionally with carriers, optionally a rate controlling barrier to deliver the compound to the skin of the host at a controlled and predetermined rate over a prolonged period of time, and means to secure the device to the skin. Matrix transdermal formulations can also be used. Suitable formulations for topical application, e.g., to the skin and eyes, are preferably aqueous solutions, ointments, creams or gels well-known in the art. Such can contain solubilizers, stabilizers, tonicity enhancing agents, buffers and preservatives.

Compounds of the invention can be administered in therapeutically effective amounts in combination with one or more therapeutic agents (pharmaceutical combinations). For example, synergistic effects can occur with other substances used in the treatment of cardiovascular, inflammatory and/or neurodegenerative diseases. Examples of such compounds include fibrates, TZDs, metformin, etc. Where the compounds of the invention are administered in conjunction with other therapies, dosages of the co-administered compounds will of course vary depending on the type of co-drug employed, on the specific drug employed, on the condition being treated and so forth.

The invention also provides for a pharmaceutical combinations, e.g. a kit, comprising a) a first agent which is a compound of the invention as disclosed herein, in free form or in pharmaceutically acceptable salt form, and b) at least one co-agent. The kit can comprise instructions for its administration.

The terms "co-administration" or "combined administration" or the like as utilized herein are meant to encompass administration of the selected therapeutic agents to a single patient, and are intended to include treatment regimens in which the agents are not necessarily administered by the same route of administration or at the same time.

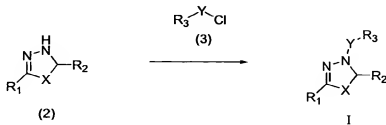
The term "pharmaceutical combination" as used herein means a product that results from the mixing or combining of more than one active ingredient and includes both fixed and non-fixed combinations of the active ingredients. The term "fixed combination" means that the active ingredients, e.g. a compound of Formula I and a co-agent, are both administered to a patient simultaneously in the form of a single entity or dosage. The term "non-fixed combination" means that the active ingredients, e.g. a compound of Formula I and a co-agent, are both administered to a patient as separate entities either simultaneously, concurrently or sequentially with no specific time limits, wherein such administration provides therapeutically effective levels of the 2 compounds in the body of the patient. The latter also applies to cocktail therapy, e.g. the administration of 3 or more active ingredients.

Processes for Making Compounds of the Invention

The present invention also includes processes for the preparation of compounds of the invention. In the reactions described, it can be necessary to protect reactive functional groups, for example hydroxy, amino, imino, thio or carboxy groups, where these are desired in the final product, to avoid their unwanted participation in the reactions. Conventional protecting groups can be used in accordance with standard practice, for example, see T.W. Greene and P. G. M. Wuts in "Protective Groups in Organic Chemistry", John Wiley and Sons, 1991.

Compounds of Formula I, in which Y is C(O), S(O) or S(O)₂ and X is S or CR₄R₅, can be prepared by proceeding as in the following Reaction Scheme I:

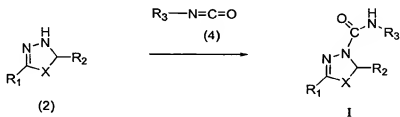
Reactions Scheme I



in which R_1 , R_2 , R_3 , R_4 , R_5 and X are as defined for Formula I in the Summary of the Invention. Compounds of Formula I are prepared by reacting a compound of formula 2 with a compound of formula 3 in the presence of a suitable solvent (e.g., dichloromethane, or the like) and a suitable base (e.g., diisopropylethylamine, or the like). The reaction is carried out in the temperature range of 10 to 40°C and takes up to 12 hours to complete.

Compounds of Formula I, in which Y is $-C(O)NHR_3$ and X is S or CR_4R_5 , can be prepared by proceeding as in the following Reaction Scheme II:

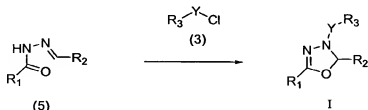
Reactions Scheme II



in which R_1 , R_2 , R_3 , R_4 , R_5 and X are as defined for Formula I in the Summary of the Invention. Compounds of Formula I are prepared by reacting a compound of formula 2 with a compound of formula 4 in the presence of a suitable solvent (e.g., ether, or the like). The reaction is carried out in the temperature range of 10 to 40°C and takes up to 6 hours to complete.

Compounds of Formula I, in which X is O , can be prepared by proceeding as in the following Reaction Scheme III:

Reactions Scheme III



in which R_1 , R_2 , R_3 , R_4 , R_5 and Y are as defined for Formula I in the Summary of the Invention. Compounds of Formula I are prepared by reacting a compound of formula 5 with a compound of formula 3 in the presence of a suitable solvent (e.g., dichloromethane, or the like)

and a suitable base (e.g., diisopropylethylamine, or the like). The reaction is carried out in the temperature range of 10 to 40°C and takes up to 12 hours to complete.

Additional Processes for Making Compounds of the Invention

5 A compound of the invention can be prepared as a pharmaceutically acceptable acid addition salt by reacting the free base form of the compound with a pharmaceutically acceptable inorganic or organic acid. Alternatively, a pharmaceutically acceptable base addition salt of a compound of the invention can be prepared by reacting the free acid form of the compound with a pharmaceutically acceptable inorganic or organic base. Alternatively, the salt forms of the
10 compounds of the invention can be prepared using salts of the starting materials or intermediates.

 The free acid or free base forms of the compounds of the invention can be prepared from the corresponding base addition salt or acid addition salt from, respectively. For example a compound of the invention in an acid addition salt form can be converted to the corresponding free base by treating with a suitable base (e.g., ammonium hydroxide solution, sodium
15 hydroxide, and the like). A compound of the invention in a base addition salt form can be converted to the corresponding free acid by treating with a suitable acid (e.g., hydrochloric acid, etc.)

 Compounds of the invention in unoxidized form can be prepared from N-oxides of compounds of the invention by treating with a reducing agent (e.g., sulfur, sulfur dioxide, triphenyl phosphine, lithium borohydride, sodium borohydride, phosphorus trichloride, tribromide, or the like) in a suitable inert organic solvent (e.g. acetonitrile, ethanol, aqueous
20 dioxane, or the like) at 0 to 80°C.

 Prodrug derivatives of the compounds of the invention can be prepared by methods known to those of ordinary skill in the art (e.g., for further details see Saulnier et al., (1994),
25 Bioorganic and Medicinal Chemistry Letters, Vol. 4, p. 1985). For example, appropriate prodrugs can be prepared by reacting a non-derivatized compound of the invention with a suitable carbamylating agent (e.g., 1,1-acyloxyalkylcarbanochloride, para-nitrophenyl carbonate, or the like).

 Protected derivatives of the compounds of the invention can be made by means known
30 to those of ordinary skill in the art. A detailed description of techniques applicable to the

creation of protecting groups and their removal can be found in T. W. Greene, "Protecting Groups in Organic Chemistry", 3rd edition, John Wiley and Sons, Inc., 1999.

Compounds of the present invention can be conveniently prepared, or formed during the process of the invention, as solvates (e.g., hydrates). Hydrates of compounds of the present invention can be conveniently prepared by recrystallization from an aqueous/organic solvent mixture, using organic solvents such as dioxin, tetrahydrofuran or methanol.

Compounds of the invention can be prepared as their individual stereoisomers by reacting a racemic mixture of the compound with an optically active resolving agent to form a pair of diastereoisomeric compounds, separating the diastereomers and recovering the optically pure enantiomers. While resolution of enantiomers can be carried out using covalent diastereomeric derivatives of the compounds of the invention, dissociable complexes are preferred (e.g., crystalline diastereomeric salts). Diastereomers have distinct physical properties (e.g., melting points, boiling points, solubilities, reactivity, etc.) and can be readily separated by taking advantage of these dissimilarities. The diastereomers can be separated by chromatography, or preferably, by separation/resolution techniques based upon differences in solubility. The optically pure enantiomer is then recovered, along with the resolving agent, by any practical means that would not result in racemization. A more detailed description of the techniques applicable to the resolution of stereoisomers of compounds from their racemic mixture can be found in Jean Jacques, Andre Collet, Samuel H. Wilen, "Enantiomers, Racemates and Resolutions", John Wiley And Sons, Inc., 1981.

In summary, the compounds of Formula I can be made by a process, which involves:

- (a) those of reaction schemes I and II; and
- (b) optionally converting a compound of the invention into a pharmaceutically acceptable salt;
- (c) optionally converting a salt form of a compound of the invention to a non-salt form;
- (d) optionally converting an unoxidized form of a compound of the invention into a pharmaceutically acceptable N-oxide;
- (e) optionally converting an N-oxide form of a compound of the invention to its unoxidized form;

(f) optionally resolving an individual isomer of a compound of the invention from a mixture of isomers;

(g) optionally converting a non-derivatized compound of the invention into a pharmaceutically acceptable prodrug derivative; and

5 (h) optionally converting a prodrug derivative of a compound of the invention to its non-derivatized form.

Insofar as the production of the starting materials is not particularly described, the compounds are known or can be prepared analogously to methods known in the art or as disclosed in the Examples hereinafter.

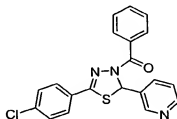
10 One of skill in the art will appreciate that the above transformations are only representative of methods for preparation of the compounds of the present invention, and that other well known methods can similarly be used.

Examples

15 The present invention is further exemplified, but not limited, by the following examples that illustrate the preparation of compounds of Formula I according to the invention.

Example 1

5-[4-Chloro-phenyl]-2-pyridin-3-yl-[1,3,4]thiadiazol-3-yl]-phenyl-methanone



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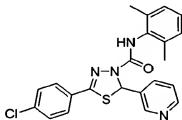
To a heterogeneous mixture of 4-chloro-thiobenzoic acid hydrazide (0.53 mmol) in CH_2Cl_2 (2 mL) is added pyridine-3-carboxaldehyde (0.55 mmol). After 10 minutes the mixture become homogenous and the reaction is complete by TLC and LCMS to give 3-[5-(4-Chloro-phenyl)-2,3-dihydro-[1,3,4]thiadiazol-2-yl]-pyridine which is used as such in the next step

25 without evaporation of the solvent.

To the solution of 3-[5-(4-Chloro-phenyl)-2,3-dihydro-[1,3,4]thiadiazol-2-yl]-pyridine is added N,N-diisopropylethyl amine (0.8 mmol) and benzoyl chloride (0.8 mmol) and the reaction mixture is stirred for 2 hours at room temperature. After concentration, the residue is purified by preparative LCMS (10 to 90% CH₃CN). ¹H NMR (400 MHz, CDCl₃) δ 9.02 (s, 1H), 8.84 (d, *J* = 4.4 Hz, 1H), 8.19 (d, *J* = 8 Hz, 1H), 8.10 (d, *J* = 8 Hz, 2H), 7.8 (d, *J* = 8.4 Hz, 2H), 7.68 (m, 6H), 7.56 (s, 1H). ¹³C NMR (400 MHz, CDCl₃) δ 167.19, 149.59, 146.58, 144.89, 137.75, 137.69, 132.95, 131.93, 129.98, 129.63, 129.26, 128.67, 128.14, 127.9, 125.16, 68.42. MS: (ES⁺) 380.0 (M+1)⁺

Example 2

5-(4-Chloro-phenyl)-2-pyridin-3-yl-[1,3,4]thiadiazole-3-carboxylic acid (2,6-dimethyl-phenyl)-amide

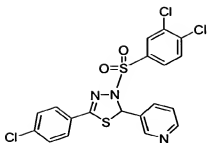


To a heterogeneous mixture of 4-Chloro-thiobenzoic acid hydrazide (0.53 mmol) in CH₂Cl₂ (2 mL) is added pyridine-3-carboxaldehyde (0.55 mmol). After 10 minutes the mixture become homogenous and the reaction is complete by TLC and LCMS to give 3-[5-(4-Chloro-phenyl)-2,3-dihydro-[1,3,4]thiadiazol-2-yl]-pyridine which is used as such in the next step after evaporation of the solvent.

To a solution of 3-[5-(4-Chloro-phenyl)-2,3-dihydro-[1,3,4]thiadiazol-2-yl]-pyridine in Et₂O (2 mL) is added 2-isocyanato-1,3-dimethyl-benzene (0.8 mmol) and the reaction mixture is stirred for 12 hours at room temperature. After concentration, the residue is purified by preparative LCMS (10 to 90% CH₃CN). ¹H NMR (400 MHz, CDCl₃) δ 8.85 (s, 1H), 8.69 (d, *J* = 5.6 Hz, 1H), 8.12 (d, *J* = 5.3 Hz, 1H), 7.68 (d, *J* = 8 Hz, 2H), 7.59 (dd, 1H), 7.47 (d, *J* = 8 Hz, 2H), 7.42 (s, 1H), 7.20 (s, 1H), 7.09 (m, 3H), 2.24 (s, 6H). MS: (ES⁺) 423.0 (M+1)⁺.

Example 3

3-[5-(4-Chloro-phenyl)-3-(3,4-dichloro-benzenesulfonyl)-2,3-dihydro-[1,3,4]thiadiazol-2-yl]-pyridine

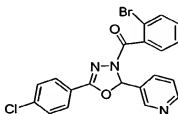


To a heterogeneous mixture of 4-chloro-thiobenzoic acid hydrazide (0.53 mmol) in CH_2Cl_2 (2 mL) is added pyridine-3-carboxaldehyde (0.55 mmol). After 10 minutes the mixture become homogenous and the reaction is complete by TLC and LCMS to give 3-[5-(4-Chloro-phenyl)-2,3-dihydro-[1,3,4]thiadiazol-2-yl]-pyridine which is used as such in the next step without evaporation of the solvent.

To the solution of 3-[5-(4-Chloro-phenyl)-2,3-dihydro-[1,3,4]thiadiazol-2-yl]-pyridine is added *N,N*-diisopropylethyl amine (0.8 mmol) and 3,4-dichlorobenzoyl chloride (0.8 mmol) and the reaction mixture is stirred for 12 h at r.t.. After concentration, the residue is purified by preparative LCMS (10 to 90% CH_3CN). ^1H NMR (400 MHz, CDCl_3) δ 8.66 (s, 1H), 8.64 (d, 1H), 7.81 (d, $J = 2\text{ Hz}$, 1H), 7.79 (m, 1H), 7.63 (m, 3H), 7.55 (s, 1H), 7.52 (d, $J = 3.2\text{ Hz}$, 1H), 7.42 (d, $J = 8.4\text{ Hz}$, 2H), 6.85 (s, 1H). MS: (ES^+) 485.9 ($\text{M}+1$) $^+$.

Example 4

(2-Bromo-phenyl)-[5-(4-chloro-phenyl)-2-pyridin-3-yl-[1,3,4]oxadiazol-3-yl]-methanone



To a solution of 4-Chloro-benzoic acid hydrazide (0.53 mmol) in EtOH (2 mL) is added pyridine-3-carboxaldehyde (0.55 mmol) and the mixture is stirred at 80 $^{\circ}\text{C}$. After 30 minutes the reaction is complete by TLC and LCMS to give 4-Chloro-benzoic acid pyridin-3-ylmethylene-hydrazide which is used as such in the next step after evaporation of the solvent.

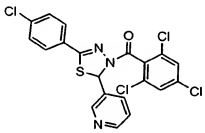
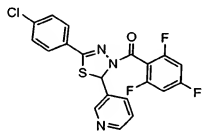
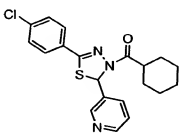
To the 4-Chloro-benzoic acid pyridin-3-ylmethylene-hydrazide is added 2-bromobenzoyl chloride (1 mL) and the reaction mixture is stirred for 2 h at 200 $^{\circ}\text{C}$. After concentration, the residue is purified by preparative LCMS (10 to 90% CH_3CN). ^1H NMR (400

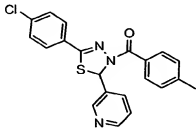
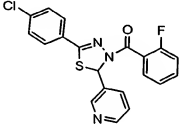
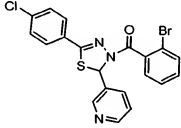
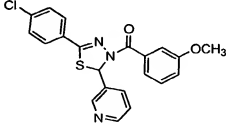
MHz, CDCl₃) δ 9.04 (s, 1H), 8.81 (d, J = 3.2 Hz, 1H), 8.23 (d, J = 5.2 Hz, 1H), 7.75 (d, J = 6 Hz, 2H), 7.64 (m, 2H), 7.37 (s, 1H), 7.42 (m, 5H). ¹³C NMR (400 MHz, CDCl₃) δ 162.7, 153.3, 145.8, 143.1, 136.1, 135.3, 133.3, 130.6, 130.4, 128.9, 126.8, 126.9, 126.1, 124.8, 122.4, 119.5, 117.7, 87.9. MS: (ES⁺) 441.9 (M+1)⁺.

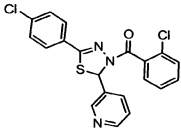
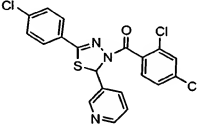
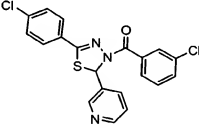
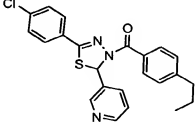
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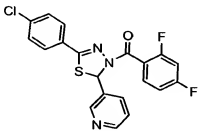
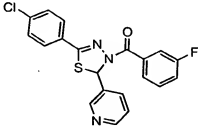
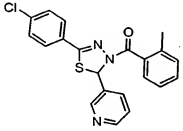
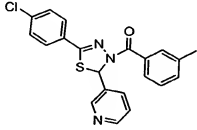
By repeating the procedures described in the above examples, using appropriate starting materials, the following compounds of Formula I, as identified in Table 1, are obtained.

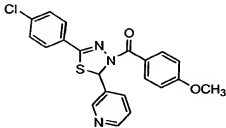
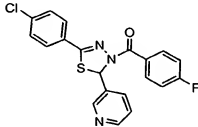
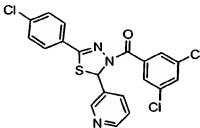
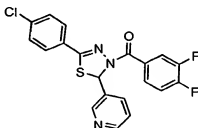
Table 1

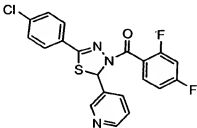
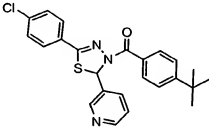
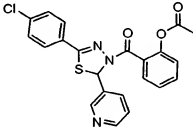
Compound Number	Structure	Physical Data ¹ H NMR 400 MHz (CDCl ₃) and/or MS (m/z)
5		481.8
6		433.9
7		386.0

Compound Number	Structure	Physical Data ¹ H NMR 400 MHz (CDCl ₃) and/or MS (m/z)
8		¹ H NMR 400MHz (CDCl ₃) δ 8.78 (s, 1H), 8.57 (d, J=4.4Hz, 1H), 7.9 (d, 2H), 7.83 (m, 1H), 7.65 (d, 2H), 7.41 (d, 2H) 7.45 (s, 1H), 7.4 (m, 1H), 7.25 (d, 2H), 7.25 (d, 2H), 2.42 (s, 3H); MS (m/z) 394.0.
9		398.0
10		457.9
11		410.0

Compound Number	Structure	Physical Data ¹ H NMR 400 MHz (CDCl ₃) and/or MS (m/z)
12		413.9
13		447.9
14		413.9
15		422.0

Compound Number	Structure	Physical Data ¹ H NMR 400 MHz (CDCl ₃) and/or MS (m/z)
16		¹ H NMR 400MHz (CDCl ₃) δ 8.7 (s, 1H), 8.57 (d, J=4.4Hz, 1H), 7.79 (m, 1H), 7.44 (d, 2H), 7.35 (dd, 1H), 7.29 (d, 2H) 7.19 (s, 1H), 7.1 (m, 1H); MS (m/z) 415.9
17		398.0
18		394.0
19		394.0

Compound Number	Structure	Physical Data ¹ H NMR 400 MHz (CDCl ₃) and/or MS (m/z)
20		410.0
21		397.9
22		447.9
23		415.9

Compound Number	Structure	Physical Data ¹ H NMR 400 MHz (CDCl ₃) and/or MS (m/z)
24		415.9
25		436.0
26		438.0

Assay1 - Transcriptional Assay

Transfection assays are used to assess the ability of compounds of the invention to modulate the transcriptional activity of the LXRs. Briefly, expression vectors for chimeric proteins containing the DNA binding domain of yeast GAL4 fused to the ligand-binding domain (LBD) of either LXR α or LXR β are introduced via transient transfection into mammalian cells, together with a reporter plasmid where the luciferase gene is under the control of a GAL4 binding site. Upon exposure to an LXR modulator, LXR transcriptional activity varies, and this can be monitored by changes in luciferase levels. If transfected cells are exposed to an LXR agonist, LXR-dependent transcriptional activity increases and luciferase levels rise.

293T human embryonic kidney cells (8×10^6) are seeded in a 175 cm^2 flask 2 days prior to the start of the experiment in 10% FBS, 1% Penicillin/Streptomycin/Fungizone, DMEM Media. The transfection mixture for chimeric proteins is prepared using GAL4-LXR LBD expression plasmid (4 μg), UAS-luciferase reporter plasmid (5 μg), Fugene (3:1 ratio; 27 μL) and serum-free media (210 μL). The transfection mixture is incubated for 20 minutes at room temperature. The cells are harvested by washing with PBS (30ml) and then dissociating using trypsin (0.05%; 3ml). The trypsin is inactivated by the addition of assay media (DMEM, lipoprotein-deficient fetal bovine serum (5%), statin (e.g. lovastatin 7.5 μM), and mevalonic acid (100 μM)) (10ml). The cells are counted using a 1:10 dilution and the concentration of cells adjusted to 160,000 cells/ml. The cells are further incubated for 30 minutes at room temperature with periodic mixing by inversion. Transfection mixtures are added to the cells, and cells (50 μL /well) are then plated into 384 white, solid-bottom, TC-treated plates. The cells are further incubated at 37°C, 5.0% CO₂ for 24 hours. A 12-point series of dilutions (half-log serial dilutions) are prepared for each test compound in DMSO with a starting concentration of compound of 1 μM . Test compound (500nl) is added to each well of cells in the assay plate and the cells are incubated at 37°C, 5.0% CO₂ for 24 hours. The cell lysis/luciferase assay buffer, Bright-Glo™ (25%; 25 μL ; Promega), is added to each well. After a further incubation for 5 minutes at room temperature, the luciferase activity is measured.

Raw luminescence values are normalized by dividing them by the value of the DMSO control present on each plate. Normalized data is visualized using XLfit3 and dose-response curves are fitted using a 4-parameter logistic model or sigmoidal single-site dose-response equation (equation 205 in XLfit3.05). EC50 is defined as the concentration at which the compound elicits a response that is half way between the maximum and minimum values. Relative efficacy (or percent efficacy) is calculated by comparison of the response elicited by the compound with the maximum value obtained for a reference LXR modulator.

Assay2 - FRET Co-activator Recruitment Assay

A FRET assay is used to assess the ability of a compound of the invention to bind directly to the LXR ligand-binding domain (LBD) and promote the recruitment of proteins that potentiate the transcriptional activity of LXRs (e.g. co-activators). This cell-free assay uses a

recombinant fusion protein composed of the LXR LBD and a tag (e.g. GST, His, FLAG) that simplifies its purification, and a synthetic biotinylated peptide derived from the nuclear receptor interacting domain of a transcriptional co-activator protein, such as steroid receptor co-activator 1 (SRC-1). In one format, the tagged LBD fusion protein can be labeled using an antibody
5 against the LBD tag coupled to europium (e.g. EU-labeled anti-GST antibody), and the co-activator peptide can be labeled with allophycocyanin (APC) coupled to streptavidin. In the presence of an agonist for LXR, the co-activator peptide is recruited to the LXR LBD, bringing the EU and APC moieties in close proximity. Upon excitation of the complex with light at 340nm, EU absorbs and transfers energy to the APC moiety resulting in emission at 665 nm. If
10 there is no energy transfer (indicating lack of EU-APC proximity), EU emits at 615nm. Thus the ratio of the 665 to 615nm light emitted gives an indication of the strength of co-activator peptide recruitment, and thus of agonist binding to the LXR LBD.

Fusion proteins, amino acids 205-447 (Genbank NM_005693) for LXR α and amino acids 203-461 (NM_007121 for β) for LXR β , were cloned in-frame at the SalI and NotI sites of
15 pGEX4T-3 (27-4583-03 Amersham Pharmacia Biotech). A biotinylated peptide sequence was derived from SRC-1 (amino acids 676 to 700): biotin-CPSSHSLTERHKILHRLQLQEGSPSC-OH.

A master mix is prepared (5nM GST-LXR-LBD, 5nM Biotinylated SRC-1 peptide, 10nM APC-Streptavidin (Prozyme Phycolink streptavidin APC, PJ25S), and 5nM MEU-Anti-GST
20 Antibody) in FRET buffer (50mM Tris pH 7.5, 50mM KCl 1mM DTT, 0.1% BSA). To each well of a 384 well plate, 20 μ L of this master mix is added. Final FRET reaction: 5nM fusion protein, 5nM SRC-1 peptide, 10nM APC-Streptavidin, 5nM EU-Anti-GST Antibody (PerkinElmer AD0064). Test compounds are diluted in half-log, 12-point serial dilutions in DMSO, starting at 1mM and 100nL of compound is transferred to the master mix for a final
25 concentration of 5 μ M-28pM in the assay wells. Plates are incubated at room temperature for 3 hours and fluorescence resonance energy transfer read. Results are expressed as the ratio of APC fluorescence to EU fluorescence times one thousand.

The ratio of 665nm to 615nm is multiplied by a factor of 1000 to simplify data analysis. DMSO values are subtracted from ratios to account for background. Data is visualized
30 using XLfit3 and dose-response curves are fitted using a 4-parameter logistic model or sigmoidal single-site dose-response equation (equation 205 in XLfit3.05). EC50 is defined as the

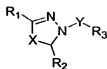
concentration at which the compound elicits a response that is half way between the maximum and minimum values. Relative efficacy (or percent efficacy) is calculated by comparison of the response elicited by the compound with the maximum value obtained for a reference LXR modulator.

5 Compounds of Formula I, in free form or in pharmaceutically acceptable salt form, exhibit valuable pharmacological properties, for example, as indicated by the *in vitro* tests described in this application.

10 It is understood that the examples and embodiments described herein are for illustrative purposes only and that various modifications or changes in light thereof will be suggested to persons skilled in the art and are to be included within the spirit and purview of this application and scope of the appended claims. All publications, patents, and patent applications cited herein are hereby incorporated by reference for all purposes.

WE CLAIM:

1. A compound of Formula I:



in which:

X is selected from the group consisting of S, O and CR₄R₅; wherein R₄ is selected from the group consisting of hydrogen and C₁₋₆alkyl; R₅ is selected from the group consisting of hydrogen, C₁₋₆alkyl, C₆₋₁₀aryl, C₅₋₁₀heteroaryl, C₃₋₁₂cycloalkyl and C₃.

heterocycloalkyl; or R₄ and R₅ together with the carbon atom to which R₄ and R₅ are attached form C₃₋₁₂cycloalkyl or C₃₋₈heterocycloalkyl; wherein any aryl, heteroaryl, cycloalkyl or heterocycloalkyl of R₅ or the combination of R₄ and R₅ is optionally substituted with 1 to 4 radicals independently selected from the group consisting of halo, hydroxy, cyano, nitro, C₁₋₆alkyl, C₁₋₆alkoxy, halo-substituted-C₁₋₆alkyl and halo-substituted-C₁₋₆alkoxy;

Y is selected from the group consisting of C(O), S(O), S(O)₂, C(O)N(R₆) and C(O)OR₆; wherein R₆ is selected from the group consisting of hydrogen, C₁₋₆alkyl, C₆₋₁₀aryl, C₅₋₁₀heteroaryl, C₃₋₁₂cycloalkyl and C₃₋₈heterocycloalkyl; wherein any aryl, heteroaryl, cycloalkyl or heterocycloalkyl of R₆ is optionally substituted with 1 to 4 radicals independently selected from the group consisting of halo, hydroxy, cyano, nitro, C₁₋₆alkyl, C₁₋₆alkoxy, halo-substituted-C₁₋₆alkyl and halo-substituted-C₁₋₆alkoxy;

R₁ is selected from the group consisting C₆₋₁₀aryl, C₅₋₁₀heteroaryl, C₃₋₁₂cycloalkyl and C₃₋₈heterocycloalkyl; wherein any aryl, heteroaryl, cycloalkyl or heterocycloalkyl of R₁ is optionally substituted with 1 to 4 radicals independently selected from the group consisting of halo, hydroxy, cyano, nitro, C₁₋₆alkyl, C₁₋₆alkoxy, halo-substituted-C₁₋₆alkyl, halo-substituted-C₁₋₆alkoxy -C(O)NR₇R₈, -OC(O)R₇, -NR₇R₈, -C(O)R₇ and -NR₇C(O)R₇; wherein R₇ and R₈ are independently chosen from hydrogen, C₁₋₆alkyl, C₁₋₆alkoxy, halo-substituted-C₁₋₆alkyl and halo-substituted-C₁₋₆alkoxy, C₆₋₁₀aryl-C₀₋₄alkyl, C₃₋₈heteroaryl-C₀₋₄alkyl, C₃₋₁₂cycloalkyl-C₀₋₄alkyl and C₃₋₈heterocycloalkyl-C₀₋₄alkyl; or R₇ and R₈ together with the nitrogen atom to which R₇ and R₈ are attached form C₅₋₁₀heteroaryl or C₃₋₈heterocycloalkyl; wherein any aryl, heteroaryl,

cycloalkyl or heterocycloalkyl of R₇ or the combination of R₇ and R₈ is optionally substituted with 1 to 4 radicals independently selected from the group consisting of halo, hydroxy, cyano, nitro, C₁₋₆alkyl, C₁₋₆alkoxy, halo-substituted-C₁₋₆alkyl and halo-substituted-C₁₋₆alkoxy;

R₂ is selected from the group consisting of C₆₋₁₀aryl, C₅₋₁₀heteroaryl, C₃₋

12cycloalkyl and C₃₋₈heterocycloalkyl; wherein any aryl, heteroaryl, cycloalkyl or heterocycloalkyl of R₂ is optionally substituted with 1 to 4 radicals independently selected from the group consisting of halo, hydroxy, cyano, nitro, C₁₋₆alkyl, C₁₋₆alkoxy, halo-substituted-C₁₋₆alkyl, halo-substituted-C₁₋₆alkoxy -C(O)NR₇R₈, -OR₇, -OC(O)R₇, -NR₇R₈, -C(O)R₇ and -NR₇C(O)R₇; wherein R₇ and R₈ are independently chosen from hydrogen, C₁₋₆alkyl, C₁₋₆alkoxy, halo-substituted-C₁₋₆alkyl and halo-substituted-C₁₋₆alkoxy, C₆₋₁₀aryl-C₀₋₄alkyl, C₃₋₈heteroaryl-C₀₋₄alkyl, C₃₋₁₂cycloalkyl-C₀₋₄alkyl and C₃₋₈heterocycloalkyl-C₀₋₄alkyl; or R₇ and R₈ together with the nitrogen atom to which R₇ and R₈ are attached form C₅₋₁₀heteroaryl or C₃₋₈heterocycloalkyl; wherein any aryl, heteroaryl, cycloalkyl or heterocycloalkyl of R₇ or the combination of R₇ and R₈ is optionally substituted with 1 to 4 radicals independently selected from the group consisting of halo, hydroxy, cyano, nitro, C₁₋₆alkyl, C₁₋₆alkoxy, halo-substituted-C₁₋₆alkyl and halo-substituted-C₁₋₆alkoxy;

R₃ is selected from the group consisting of C₆₋₁₀aryl, C₅₋₁₀heteroaryl, C₃₋

12cycloalkyl and C₃₋₈heterocycloalkyl; wherein any aryl, heteroaryl, cycloalkyl or heterocycloalkyl of R₃ is optionally substituted with 1 to 4 radicals independently selected from the group consisting of halo, hydroxy, cyano, nitro, C₁₋₆alkyl, C₁₋₆alkoxy, halo-substituted-C₁₋₆alkyl, halo-substituted-C₁₋₆alkoxy -C(O)NR₇R₈, -OC(O)R₇, -NR₇R₈, -C(O)R₇ and -NR₇C(O)R₇; wherein R₇ and R₈ are independently chosen from hydrogen, C₁₋₆alkyl, C₁₋₆alkoxy, halo-substituted-C₁₋₆alkyl and halo-substituted-C₁₋₆alkoxy, C₆₋₁₀aryl-C₀₋₄alkyl, C₃₋₈heteroaryl-C₀₋₄alkyl, C₃₋₁₂cycloalkyl-C₀₋₄alkyl and C₃₋₈heterocycloalkyl-C₀₋₄alkyl; or R₇ and R₈ together with the nitrogen atom to which R₇ and R₈ are attached form C₅₋₁₀heteroaryl or C₃₋₈heterocycloalkyl; wherein any aryl, heteroaryl, cycloalkyl or heterocycloalkyl of R₇ or the combination of R₇ and R₈ is optionally substituted with 1 to 4 radicals independently selected from the group consisting of halo, hydroxy, cyano, nitro, C₁₋₆alkyl, C₁₋₆alkoxy, halo-substituted-C₁₋₆alkyl and halo-substituted-C₁₋₆alkoxy; and the pharmaceutically acceptable salts, hydrates, solvates and isomers thereof.

2. The compound of claim 1 in which Y is selected from the group consisting of C(O) and S(O)₂ and R₁ is C₆₋₁₀aryl; wherein any aryl, heteroaryl, cycloalkyl or heterocycloalkyl of R₁ is optionally substituted with 1 to 4 radicals independently selected from the group consisting of halo, C₁₋₆alkyl, C₁₋₆alkoxy, halo-substituted-C₁₋₆alkyl and halo-substituted-C₁₋₆alkoxy.

5

3. The compound of claim 2 in which R₂ is selected from the group consisting of C₆₋₁₀aryl and C₅₋₁₀heteroaryl; wherein any aryl or heteroaryl of R₂ is optionally substituted with 1 to 3 radicals independently selected from the group consisting of halo, hydroxy, cyano, nitro, C₁₋₆alkyl, C₁₋₆alkoxy, halo-substituted-C₁₋₆alkyl and halo-substituted-C₁₋₆alkoxy.

10

4. The compound of claim 3 in which R₃ is selected from the group consisting of C₆₋₁₀aryl and C₃₋₁₂cycloalkyl; wherein any aryl or cycloalkyl of R₃ is optionally substituted with 1 to 3 radicals independently selected from the group consisting of halo, -OC(O)R₇, C₁₋₆alkyl and C₁₋₆alkoxy; wherein R₇ is chosen from hydrogen, C₁₋₆alkyl, C₁₋₆alkoxy, halo-substituted-C₁₋₆alkyl and halo-substituted-C₁₋₆alkoxy, C₆₋₁₀aryl-C₀₋₄alkyl, C₃₋₈heteroaryl-C₀₋₄alkyl, C₃₋₁₂cycloalkyl-C₀₋₄alkyl and C₃₋₈heterocycloalkyl-C₀₋₄alkyl.

15

5. The compound of claim 1 in which X is S.

20

6. The compound of claim 1 in which R₁ is phenyl optionally substituted with 1 to 4 radicals independently selected from the group consisting of halo, C₁₋₆alkyl, C₁₋₆alkoxy, halo-substituted-C₁₋₆alkyl and halo-substituted-C₁₋₆alkoxy.

25

7. The compound of claim 1 in which R₂ is selected from the group consisting of phenyl and pyridinyl; wherein any aryl or heteroaryl of R₂ is optionally substituted with 1 to 3 radicals independently selected from the group consisting of halo, C₁₋₆alkyl, C₁₋₆alkoxy, halo-substituted-C₁₋₆alkyl and halo-substituted-C₁₋₆alkoxy.

30

8. The compound of claim 1 in which R₃ is selected from the group consisting of phenyl and cyclohexyl; wherein any aryl or cycloalkyl of R₃ is optionally substituted with 1 to 3

radicals independently selected from the group consisting of halo, -OC(O)CH₃, methyl, ethyl, propyl, isopropyl, butyl, tert-butyl and OCH₃.

5 9. A pharmaceutical composition comprising a therapeutically effective amount of a compound of Claim 1 in combination with a pharmaceutically acceptable excipient.

10 10. A method for treating a disease in an animal in which modulation of LXR activity can prevent, inhibit or ameliorate the pathology and/or symptomology of the disease, which method comprises administering to the animal a therapeutically effective amount of a compound of Claim 1.

15 11. The use of a compound of claim 1 in the manufacture of a medicament for treating a disease in an animal in which LXR activity contributes to the pathology and/or symptomology of the disease.

**COMPOUNDS AND COMPOSITIONS AS
LXR MODULATORS**

5

ABSTRACT OF THE DISCLOSURE

10 The invention provides compounds, pharmaceutical compositions comprising such
compounds and methods of using such compounds to treat or prevent diseases or disorders
associated with the activity of liver X receptors (LXRs).